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Award Number: DAMD17-02-1-0569

TITLE: Evaluation of DNA Methylation as a Target for Intraductal Therapy for Ductal Carcinoma In Situ of the Breast

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REPORT DATE: August 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2003	Annual (15 Jul 2002 - 15 Jul 2003)

4. TITLE AND SUBTITLE
Evaluation of DNA Methylation as a Target for Intraductal Therapy for Ductal Carcinoma In Situ of the Breast

5. FUNDING NUMBERS
DAMD17-02-1-0569

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

Ductal carcinoma *in situ*(DCIS), the preinvasive form of infiltrating ductal breast cancer, accounts for 20-30% of breast cancers and is treated surgically. In DCIS, the malignant cells are confined within the basement membrane. DCIS is a local disease, and so an ideal candidate for local therapies. DNA methylation is one mechanism for tumor suppressor gene inactivation. It is an early event in the course of malignant progression. Because methylation is a potentially reversible mechanism for tumor suppressor gene inactivation, it is an intriguing target for molecular therapeutics. Drugs, such as 5-aza-deoxycytidine (DAC), are available that can reverse methylation changes and prevent neoplasia *in vivo*. **Hypothesis: DNA Methylation is altered in DCIS and is a therapeutic target for intraductal therapy. Specific Aim 1: D**ocument the methylation status of tumor suppressor genes in DCIS. **Specific Aim 2:** Document the feasibility of an intraductal approach to DCIS. **Specific Aim 3:** Identify the dose(s) of DAC with biologic activity and acceptable side effects when delivered intraductally to patients with DCIS (Phase I trial). The ultimate goal of this proposal is to evaluate DNA methylation as a target for intraductal therapy. The results of this study could revolutionize the way we treat DCIS.

14. SUBJECT TERMS
Ductal Carcinoma in situ of the Breast, intraductal therapy, ductal Lavage, DNA methylation, 5-aza-2'-deoxycytidine, decitidine

15. NUMBER OF PAGES
4

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Introduction: Ductal carcinoma *in situ*(DCIS), the preinvasive form of infiltrating ductal carcinoma of the breast, currently accounts for 20-30% of breast cancers and is treated by surgically removing the involved ducts. In DCIS, the malignant cells have not having invaded through the basement membrane and therefore have not gained access to the lymphatics or the systemic circulation. DCIS is a local disease, and so an ideal candidate for local therapies. DNA methylation is one mechanism for tumor suppressor gene inactivation. It is an early event in the course of malignant progression in several tumor systems. Because methylation is a potentially reversible mechanism for tumor suppressor gene inactivation, it is an intriguing target for molecular therapeutics. Drugs, such as 5-aza-deoxycytidine (DAC), are available that can reverse methylation changes and prevent tumor suppressor gene-related neoplasia *in vivo*. **Hypothesis: DNA Methylation is altered in DCIS and is a therapeutic target for intraductal therapy. Specific Aim 1:** To document the methylation status of a panel of tumor suppressor genes in DCIS. **Specific Aim 2:** Document the feasibility of an intraductal approach to DCIS. **Specific Aim 3:** Identify a dose or range of doses of DAC with biologic activity and acceptable side effects when delivered intraductally to patients with DCIS (Phase I trial). The ultimate goal of this proposal is to evaluate DNA methylation as a target for intraductal therapy. The results of this study could revolutionize the way we treat DCIS.

Body: Unfortunately due to significant administrative delays, no work has yet been done on this project. Despite a complete submission and completion of the responses to the Memorandum of Record from the HSRRB, no further action was taken by the original Human Subjects Protection Specialist assigned to my proposal, Margaret Abramowitz, RN. In 12/02 I was notified by Andrea Kline, the newly assigned Human Subjects Protection Specialist, that Ms. Abramowitz had nod presented my proposal and responses to the memorandum of record to the HSSRB. Ms. Kline confirmed that my file was complete and ready to go to the board. I notified Ms. Kline of my plans to change institutions and that I had initiated the process for transferring my grant to New York University. It was agreed to wait for the transfer prior to submitting my proposal to the HSRRB as the transfer would lead to a need for a new approval. The transfer process was initiated at the University of Southern California in 11/02. I left that institution on 12/31/02 and started at NYU in 01/03. To date, the transfer has not been completed and the proposal has not been given final approval by your HSRRB. Consequently, I have not been able to start the project. I am hopeful that this will be achieved in the next month or two and work can begin. Because of the delays, I am requesting an 18 month no cost extension in order to successfully complete the work.

Key Research Accomplishments:

-Response to Memorandum of Record Complete 8/12/02.

-No further action by Margaret Abramowitz, RN, Human Subjects Protection Specialist, AMDEX Corp.

-12/02 Notified by Andrea Kline of Change in Human Subjects Protection Specialist from AMDEX. Told that previous specialist had never forwarded my file to the Board for review. Acknowledged that my file was complete. Ms. Kline notified of my planned move and agreed to wait until transfer granted to submit to board.

-11/15/02 Began process of transferring grant as PI moving to NYU as of 1/1/03

-As of 8/1/03 Grant transfer not yet accomplished

Reportable Outcomes: None

Conclusions: No work accomplished due to administrative delays. Request 18 month no-cost extension in order to complete the project.

References: N/A

Appendices: N/A